



ISSN: 2230-9926

Available online at <http://www.journalijdr.com>

IJDR

International Journal of Development Research

Vol. 11, Issue, 11, pp. 51644-51647, November, 2021

<https://doi.org/10.37118/ijdr.23245.11.2021>



RESEARCH ARTICLE

OPEN ACCESS

CLINICAL ASPECTS OF CHILDREN WITH CYSTIC FIBROSIS AND SARS-COV-2 INFECTION: A COHORT STUDY IN A REFERRAL CENTER IN NORTHEASTERN BRAZIL

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ARTICLE INFO

Article History:

Received 25th August, 2021
Received in revised form
03rd September, 2021
Accepted 06th October, 2021
Published online 23rd November, 2021

Key Words:

COVID-19,
Cystic fibrosis,
SARS-CoV-2.

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ABSTRACT

Introduction: People with Cystic Fibrosis (CF) have a reduced life expectancy especially because of respiratory infections. Patients with CF are included in the group of people at higher risk of severe disease mediated by Coronavirus 19 (COVID-19). Therefore, the understanding of SARS-CoV-2 infection in children with CF is of fundamental importance to provide accurate guidance to parents for the risks of this disease. **Objectives:** To describe the clinical aspects of children with CF infected with SARS-Cov-2. **Methodology:** This is a cohort and descriptive study of children with CF from 0 to 18 years old. The study was based on the collection of nasopharyngeal secretions for the polymerase chain reaction/Sars-Cov-2 test. **Results:** Forty-three children with CF were evaluated. Of these, 17 (39.5%) were positive and 26 (60.5%) negative for Sars-Cov-2. Most children had a mild illness with 100% of them not hospitalized and 85.7% of hospitalized children recovered. **Conclusion:** The results suggest that children with CF infected with SARS-CoV-2 are symptomatic and despite requiring hospitalization, they have a favorable clinical course with a good prognosis in those who do not have preexisting severe lung disease.

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Citation: Fábía Regina dos Santos, Daniela Gois Meneses, Ricardo Queiroz Gurgel, Diana Matos Euzébio, Flávia Oliveira Costa, Djane Araújo Oliveira, Andréa Silva Mangabeira Lordelo, Alexia Ferreira Rodrigues, Cliomar Alves dos Santos, Angela Maria Silva. "Clinical aspects of children with cystic fibrosis and sars-cov-2 infection: a cohort study in a referral center in northeastern Brazil", *International Journal of Development Research*, 11, (11), 51644-51647.

INTRODUCTION

People with Cystic Fibrosis (CF) have a reduced life expectancy especially because of respiratory infections (FAINARDI *et al.*, 2020). A severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) is capable of producing a cytokine storm and acute respiratory distress syndrome, increasing the risk of death. CF patients also trigger cytokine dysfunction and hyperinflammation that overlap the coronavirus pathophysiology (PECKHAM *et al.*, 2020). Hypothetically, these patients should be considered to have an increased risk of developing severe manifestations when infected with SARS-CoV-2. In March 2020, the World Health Organization (WHO) announced the coronavirus disease in 2019 (Covid-19) as a

public health emergency of international concern, becoming the most lethal pandemic of modern times, mainly due to the development of severe respiratory syndrome in susceptible people (MONDEJAR-LOPEZ *et al.*, 2020; NINO *et al.*, 2021). Comorbidities such as heart disease, hypertension, diabetes, respiratory problems have a worse prognosis in the evolution of the disease caused by Coronavirus (CHAVES *et al.*, 2020). CF is a chronic autosomal recessive genetic disease caused by a mutation in the Cystic Fibrosis Transmembrane Conductance Regulator gene (CFTR) (ATHANAZIO *et al.*, 2017). It is characterized by the involvement of multiple organs, especially the gastrointestinal and pulmonary systems (HORTENCIO *et al.*, 2015). Pulmonary dysfunction plays a major role in the morbidity and mortality of CF patients (MAUCH *et al.*, 2016). According to the guidelines of the Centers for Disease Control and Prevention, patients

with CF are included in the group of people at higher risk of severe disease mediated by COVID-19 (BERARDIS *et al.*, 2020). Therefore, it is of fundamental importance to understand COVID-19 in children with CF for planning strategies to reduce the effect of the disease, in addition to providing precise guidance to parents regarding the risks of this disease. Among CF patients, respiratory viruses are associated with pulmonary exacerbations, a decline in lung function, and a risk of death (MANTI *et al.*, 2020). To date, there are limited data on the response of patients to COVID-19 infection, particularly children with CF, although preliminary information suggests that the course of the disease may be milder than expected. Given this knowledge gap, we proposed to describe the clinical aspects of children with cystic fibrosis infected with SARS-CoV-2

METHODOLOGY

This is a descriptive cohort study of children with cystic fibrosis, between 0 and 18 years old, followed at the Cystic Fibrosis Outpatient Clinic of University Hospital of Sergipe, from May 2020 to September 2021. SARS-CoV-2 was detected through a polymerase chain reaction (PCR) test performed on nasopharyngeal secretion. We collected the samples during patient follow-up visits, regardless of the presence of symptoms, as long as their guardians consented to the collection by signing the free and informed consent form. According to the results, the patients were divided into two groups: Group I - children infected with SARS-CoV-2 and Group II - children not infected with SARS-CoV-2. Demographic and clinical variables: age, race, gender, origin, salary income, genotype, symptoms, medications used, number of hospitalizations, the occurrence of exacerbation associated with Covid-19, pulmonary microbiology in the 12 months before the infection, forced expiratory volume (FEV1), body mass index (BMI), weight and height were obtained from medical records during the clinical evaluation of the children.

Data analysis: The results were summarized in tables with results in absolute and relative frequencies for categorical variables and through median and interquartile range (IQR) values (25th percentile; 75th percentile) for continuous variables. Data were analyzed using the R version 3.6.3 environment. To compare proportions between two groups and their categorical variables, we used Fisher's exact test and the chi-square test of adherence to verify the difference between frequencies in a single column. The significance level adopted was 5%.

RESULTS

Forty-three children with CF and SARS-CoV-2 infection were evaluated at a referral center in northeastern Brazil. Of these, 17 (39.5%) had the infection and 26 (60.5%) had a negative PCR for SARS-CoV-2.

Demographic data: Table 1 shows two groups: patients with and without SARS CoV-2 infection. We found that there were no significant differences between the groups. Most children were female (58.8%), from the interior of the state (76.5%) with a family income equal to or less than 1 minimum wage.

Symptomatology and management of children with SARS-CoV-2: As Table 2 shows, 70% of children infected with SARS-CoV-2 were symptomatic. The most present symptoms were onset or worsening of cough (52.9%), onset or worsening of dyspnea and loss of appetite (35.3%), fever (23.5%) among others. As for the level of care, the group without infection was not hospitalized during the period, and 41.2% of those infected were hospitalized.

Association of clinical characteristics and treatment of children with CF and hospitalization for SARS-CoV-2: Tables 3 and 4 compared the clinical characteristics and treatment of hospitalized and non-hospitalized children summarized. The frequency of hospitalization was similar when evaluating gender, genotypes, and pulmonary bacterial colonization in the last 12 months.

Hospitalized children had a median pp FEV1 51 (51.5-50.5) lower than non-hospitalized children 74 (80-71) and median BMI 15 (51.5-50.5), with the majority of eutrophic children having only a child showing thinness. The hospitalized group was younger with a median age of 0.52 years (5.8-0.3), and the age group below 1 year was the most affected. Of these, 100% had symptoms (100% onset or worsening of cough, 85.7% onset or worsening of dyspnea, and loss of appetite). Hospitalized patients (n=7) had more than one hospitalization period, totaling 12 episodes with a median time of 15 days. The most used medications were intravenous (83.3%), oral (75%), and steroids (33%) antibiotics. Of these, 41.7% of the children needed new support or increased oxygen, and 16.7% needed care in the Intensive Care Unit (ICU). In 100% of non-hospitalized children and 85.7% of hospitalized children, they recovered. Only one child died. During the study period, a child with pp FEV1 24% and presenting thinness died nine months after the first infection with Covid-19. He had 4 episodes of hospitalizations with a median duration of 40 days, two of them were in the ICU. In three admissions, he presented positive RT-PCR for SARS-CoV-2. He used broad-spectrum antibiotic therapy, oxygen therapy, and non-invasive ventilation.

DISCUSSION

We present data from 43 children with CF evaluated for SARS-CoV-2 infection at a referral center in northeastern Brazil. As far as we know, this is the first study carried out in a single and representative center of a Brazilian state in which 88.6% of children were evaluated, including asymptomatic children, most of them with a low income. Studies show that the disease tends to be more severe (MARTINS-FILHO *et al.*, 2021). Most children had a mild illness with 100% of them not hospitalized and 85.7% of hospitalized children recovered. According to available studies (POLI *et al.*, 2020), it is not known why children have a low incidence and a better prognosis of the disease. It may be due to the high plasticity of their immune system, low expression of angiotensin receptors, or exposure to other coronaviruses that are common in children. According to PECKHAM *et al.*, 2020 another hypothesis is that the induction of autophagy, increased in CF, can neutralize SARS-CoV-2 infection, although data remain limited. Children infected with SARS-CoV-2 had significant symptoms (70.6%) compared to asymptomatic non-infected children (84.6%), characterized by onset or worsening of cough (52.9%), onset or worsening of dyspnea and loss of appetite (35.3%), fever (23.5%) weight loss, malaise, fatigue or lethargy, sore throat and gastrointestinal symptoms (17.6%).

In a study by BAIN *et al.*, 2020 among the symptoms found in children with CF infected with Covid-19, fever (73%) and altered cough (72%) were the most common characteristics, with 23% presenting gastrointestinal symptoms. Other less frequently reported symptoms were fatigue, headache, and rhinitis. Our findings are in agreement with symptoms found in other studies, except for the fever, which despite being present, the percentage was lower than other symptoms. The findings of our study suggest that SARS-CoV-2 infection increases the need for hospitalization (41.2%) in CF patients. However, it has a favorable clinical course, a high recovery rate (100% of non-hospitalized children and 85.7% of hospitalized), and low mortality. The most used medications were oral antibiotics (75%), intravenous (83.3%), and steroids (33%). Of these, 41.7% of patients needed new support or increased oxygen, and 16.7% needed care in the ICU. In a study conducted in three main pediatric inpatient centers in Oman (AL YAZIDI; AL MASKARI; AL REESI, 2021) only three children with CF (3/233; 1.3%) were hospitalized for Covid-19. One child required oxygen supplementation through noninvasive ventilation and monitoring in an intensive care unit. The two other children were hospitalized and treated with a mild illness. In our research, despite having more hospitalizations compared to other studies, we observed that the prognosis seems to be very good, with recovery in most of the cases, as also shown in other studies.

Table 1. Demographic data of children with CF and SARS CoV -2 infection

	SARS CoV-2 infection n= 17 (39.5%)	No SARS CoV-2 infection n=26 (60.5%)	p-value
Gender			1.000
Female	10 (58.8%)	15 (57.7%)	
Male	7 (41.2%)	11 (42.3%)	
Median Age (IQR)	6.08 (10.4-0,5)	6.23 (10.4-4,2)	0.244
0 to 1	6 (35.3%)	3 (11.5%)	
2 to 4	2 (11.8%)	8 (30.8%)	
5 to 12	7 (41.2%)	12 (46.2%)	
13 to 18	2 (11.8%)	3 (11.5%)	
Skin color			0.343
Black	1 (5.9%)	0 (0.0%)	
Brown	9 (52.9%)	11 (42.3%)	
White	7 (41.2%)	15 (57.7%)	
Origin			0.413
Capital	4 (23.5%)	3 (12.0%)	
Interior	13 (76.5%)	23 (88.0%)	
Education level			0.629
Illiterate	8 (47.1%)	8 (30.8%)	
Elementary School	8 (47.1%)	16 (61.5%)	
High School	1 (5.8 %)	2 (7.7%)	
Income (Minimum wage)			0.310
Up to 1	10 (58.8%)	20 (77.0%)	
≥ 1	7 (41.2%)	6 (23.0%)	

Abbreviations: IQR: interquartile range

Table 2. Symptomatology and management of children with SARS-CoV-2

	SARS-CoV-2 infection n= 17 (39,5%)	No SARS-CoV-2 infection n=26 (60,5%)	p-value
Symptomatology			0.0003
Asymptomatic	5 (29.4%)	22 (84.6%)	
Symptomatic	12 (70.6%)	4 (15.4%)	
Symptoms			0.774
Fever	4 (23.5%)	0 (0.0%)	
Onset or worsening of dyspnea	6 (35.3%)	0 (0.0%)	
Onset or worsening of cough	9 (52.9%)	3 (11.5%)	
Loss of appetite	6 (35.3%)	0 (0.0%)	
Weight loss	3 (17.6%)	0 (0.0%)	
Malaise, fatigue or lethargy	3 (17.6%)	0 (0.0%)	
Sore throat	2 (11.8%)	0 (0.0%)	
Gastrointestinal symptoms	3 (17.6%)	0 (0.0%)	
Medication in use			0.103
Antivirals	0 (0.0%)	0 (0.0%)	
Antibiotics	4 (23.5%)	7 (26.9%)	
Corticosteroids	0 (0.0%)	8 (30%)	
Level of care			0.000604
Hospitalization	7 (41.2%)	0 (0.0%)	
Home care	10 (58.8%)	12 (100.0%)	

Table 3. Association of CF disease characteristics and hospitalization by Covid-19

	Hospitalized n= 7(41,2%)	Not hospitalized n=10 (58.8%)	p-value
Gender			1.00
Female	4 (57.14%)	6 (60.00%)	
Male	3 (42.86%)	4(40.00%)	
Age: median years (IQR)	0.52 (5.8 – 0.3)	8.31 (11.2-3.7)	0.034
0 to 1	5 (71.435)	1 (10.0%)	
2 to 4	0 (0.00%)	2 (20.0%)	
5 to 12	1 (14.29%)	6 (60.0%)	
13 to 18	1 (14.29%)	1 (10.0%)	
CFTR Genotypes			0.604
Homozygote F508del	1 (14.3%)	4 (40.0%)	
Heterozygous F508del	2 (28.6%)	3 (30.0%)	
Others	4 (57.1%)	3 (30.0%)	
Comorbidities			1.000
Pancreatic Insufficiency	6 (85.7)	10 (100.0%)	
CF related diabetes	0 (0.0%)	0 (0.0%)	
Liver disease	0 (0.0%)	0 (0.0%)	
Microbiological classification (colonization in the last 12 months)			0.456
Uncolonized	3 (42.9%)	3 (30.0%)	
Staphylococcus Aureus	3 (42.9%)	6 (60.0%)	
Pseudomonas Aeruginosa	0 (0.0%)	3 (30.0%)	
Median FuncPulm (pp FEV1)	51 (51.5-50.5)	74 (80-71)	0.143
>70	0 (0.0%)	4 (80.0%)	
40 to 70	2 (100.0%)	1 (20.0%)	
<40	0 (0.0%)	0 (0.0%)	
Median BMI	15 (16.0-13.7)		0.669
Thinness	1 (14.3%)	0 (0.0%)	
Eutrophy	6 (85.7%)	9 (90.0)	
Overweight risk	0 (0.0%)	0 (0.0%)	

Abbreviations: CFTR: cystic fibrosis transmembrane conductance regulator; ppFEV1: percentage of forced expiratory volume in one second; IQR: interquartile range; BMI: body mass index

Table 4. Symptomatology, treatment of children with CF, and hospitalization for SARS-CoV-2

	Hospitalized n= 7(41.2%)	Not hospitalized n=10 (58,8%)	p-value
Symptomatology			0.044
Asymptomatic	0 (0.0%)	5 (50.0%)	
Symptomatic	7 (100.0%)	5 (50.0%)	
Symptoms			0.233
Fever	2(28.6%)	2 (20.0%)	
Onset or worsening of dyspnea	6 (85.7%)	0 (0.0%)	
Onset or worsening of cough	7(100.0%)	2 (20.0%)	
Loss of appetite	6 (85.7%)	0 (0.0%)	
Weight loss	3 (42.9%)	0 (0.0%)	
Malaise, fatigue or lethargy	2 (28.6%)	1 (10.0%)	
Sore throat	1 (14.3%)	1 (10.0%)	
Gastrointestinal Symptoms	2 (28.6%)	1 (10.0%)	
Hospitalization Times = 15 daysIQR(19,5-8)			
Inpatient ICU	Yes	No	0.020
	2 (16.7%)	10 (83.3%)	
Medicines used in hospitalization	Yes	No	0.001
IV antibiotic	10 (83.3%)	2 (16.7%)	
Oral antibiotic	9 (75.0%)	3 (25.0%)	
Antivirals	4 (33.3%)	8 (66.7%)	
Systemic Corticoid	6 (50.0%)	6 (50.0%)	
Other treatments for covid	1 (8.3%)	11(91.7%)	
Immunomodulators	0 (0.0%)	0 (0.0%)	
Respiratory support in hospitalized patients	Sim	Não	0.0307
New or increased oxygenation	5 (41.7%)	7 (58.3%)	
New or increased non-invasive ventilation	1 (8.3%)	11 (91.7%)	
Invasive Ventilation (mechanical/IOT)	0 (0.0%)	12 (100.0%)	
Recovered	6 (85.7%)	12 (100.0)	
Dead	1 (14.3%)	0 (0.0%)	

Hospitalized children had a median pp FEV1 51 (51.5-50.5) lower than non-hospitalized children 74 (80-71) and a median BMI of 15 (51.5-50.5), most of them being eutrophic. The child who died had a very severe obstructive ventilatory disorder and was thin. These data suggest that SARS-CoV-2 infection in children with CF has a favorable clinical course with a good prognosis in those who do not have preexisting severe lung disease.

CONCLUSION

This study described the clinical characteristics of a cohort of children with CF evaluated for SARS-CoV-2 infection. The results suggest that children with CF infected by SARS-COV-2 are symptomatic and despite requiring hospitalization, they have a favorable clinical course with a good prognosis in those who do not have preexisting severe lung disease. Future studies are needed in a larger group of children with CF to assess the effects of SARS-COV-2 on lung function and nutritional status in these patients.

Study limitation: The number of children with CF evaluated in the Covid-19 infection cohort is small. We need more studies with a larger quantity for definitive conclusions.

Acknowledgments: We thank everyone who contributed to the development of this study

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